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Abstract: Background. Additional studies are required to identify risk factors for hepatitis C virus (HCV) transmission to health care workers after occupational exposure to HCV. Methods. We conducted a matched case-control study in 5 European countries from 1 January 1991 through 31 December 2002. Case patients were health care workers who experienced seroconversion after percutaneous or mucocutaneous exposure to HCV. Control subjects were HCV-exposed health care workers who did not experience seroconversion and were matched with case patients for center and period of exposure. Results. Sixty case patients and 204 control subjects were included in the study. All case patients were exposed to HCV-infected fluids through percutaneous injuries. The 37 case patients for whom information was available were exposed to viremic source patients. As risk factors for HCV infection, multivariate analysis identified needle placement in a source patient's vein or artery (odds ratio [OR], 100.1; 95% confidence interval [CI], 7.3-1365.7), deep injury (OR, 155.2; 95% CI, 7.1-3417.2), and sex of the health care worker (OR for male vs. female, 3.1; 95% CI, 1.0-10.0). Source patient HCV load was not introduced in the multivariate model. In unmatched univariate analysis, the risk of HCV transmission increased 11-fold for health care workers exposed to source patients with a viral load >6 log₁₀ copies/mL (95% CI, 1.1-114.1), compared with exposures to source patients with a viral load ≤4 log₁₀ copies/mL. Conclusion. In this study, HCV occupational transmission was found to occur after percutaneous exposures. The risk of HCV transmission after percutaneous exposure increased with deep injuries and procedures involving hollow-bore needle placement in the source patient's vein or artery. These results highlight the need for widespread adoption of needlestick-prevention devices in health care settings, together with other preventive measures

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Risk Factors for Hepatitis C Virus Transmission to Health Care Workers after Occupational Exposure: A European Case-Control Study

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Background. Additional studies are required to identify risk factors for hepatitis C virus (HCV) transmission to health care workers after occupational exposure to HCV.

Methods. We conducted a matched case-control study in 5 European countries from 1 January 1991 through 31 December 2002. Case patients were health care workers who experienced seroconversion after percutaneous or mucocutaneous exposure to HCV. Control subjects were HCV-exposed health care workers who did not experience seroconversion and were matched with case patients for center and period of exposure.

Results. Sixty case patients and 204 control subjects were included in the study. All case patients were exposed to HCV-infected fluids through percutaneous injuries. The 37 case patients for whom information was available were exposed to viremic source patients. As risk factors for HCV infection, multivariate analysis identified needle placement in a source patient's vein or artery (odds ratio [OR], 100.1; 95% confidence interval [CI], 7.3–1365.7), deep injury (OR, 155.2; 95% CI, 7.1–3417.2), and sex of the health care worker (OR for male vs. female, 3.1; 95% CI, 1.0–10.0). Source patient HCV load was not introduced in the multivariate model. In univariate analysis, the risk of HCV transmission increased 11-fold for health care workers exposed to source patients with a viral load $>6 \log_{10}$ copies/mL (95% CI, 1.1–114.1), compared with exposures to source patients with a viral load $\leq 4 \log_{10}$ copies/mL.

Conclusion. In this study, HCV occupational transmission was found to occur after percutaneous exposures. The risk of HCV transmission after percutaneous exposure increased with deep injuries and procedures involving hollow-bore needle placement in the source patient's vein or artery. These results highlight the need for widespread adoption of needlestick-prevention devices in health care settings, together with other preventive measures.

Infection with hepatitis C virus (HCV) is an important occupational hazard for health care workers. In longitudinal studies, attempts have been made to assess

the risk of infection associated with occupational exposures to HCV in the health care setting. In these studies, transmission rates ranged from 0% (in 9 of 25 studies) to 10.3% [1–11], with an average rate of 0.5% [12]. The specific reasons for this substantial variation in transmission rates and the factors that affect the risk of HCV infection have not been determined.

There are no approved methods for preventing HCV infection after exposure. However, the identification of factors determining an increased risk of HCV transmission would be important for postexposure coun-

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selling and management. For example, there is recent evidence that an early course of therapy during acute HCV-associated hepatitis might be associated with a larger proportion of resolved infections [13]. Aggressive follow-up schedules based on HCV RNA testing have therefore been proposed to detect occupational HCV infection as early as possible for an early course of therapy [14, 15]. However, routine HCV RNA testing of every health care worker exposed to an HCV-positive source would be costly, and its yield would be low [16, 17]. In contrast, HCV RNA testing of workers subject to occupational exposures who are at high risk of HCV transmission may be of interest.

To establish which occupational exposures may lead to HCV transmission and elaborate recommendations for their management, we conducted an incident case-control study to identify risk factors for the transmission of HCV to health care workers after occupational exposure to HCV-infected blood or body fluids.

PATIENTS AND METHODS

Definitions. Case patients were health care workers with a documented occupational exposure (i.e., percutaneous or mucocutaneous exposure) to blood or infectious body fluids from an anti-HCV antibody (anti-HCV)-positive source, with no other reported concurrent exposure to HCV, who were anti-HCV negative at the time of exposure, and who had evidence of HCV seroconversion within 6 months after exposure. Control subjects were health care workers who had a documented occupational exposure (i.e., percutaneous or mucocutaneous exposure) to blood or infectious body fluids from an anti-HCV-positive source but were anti-HCV negative at the time of exposure and at least 6 months later. In all of the countries that participated in this study, serological testing for anti-HCV was performed using commercial EIAs of the second or third generation, as available in that country at the time of the exposure. Health care workers who were found to be anti-HCV positive at baseline or at follow-up underwent confirmation with recombinant immunoblotting and/or testing of plasma samples for HCV RNA.

Identification of case patients and control subjects. Case patients were identified through voluntary reports to national or regional systems for surveillance of occupational infections in France, Italy, Spain, Switzerland, and the United Kingdom during the 12-year period from 1 January 1991 through 31 December 2002. At each health care center reporting a case, physicians in charge of occupational health were required to identify 4 control subjects in the center's data set. Control subjects were matched to case patients by the center in which the case had been exposed and by the period of exposure (i.e., the control subject's exposure was required to be within 1 year of the corresponding case patient's exposure). In some centers, >4 case patients were identified with exposures

that had occurred within 1 year of the corresponding case patient's exposure. In this situation, among all eligible control subjects, 4 control subjects having the closest exposure date to the case's exposure date were asked to be enrolled. Assuming an exposure rate of 30% among control subjects (as was reported for exposure to a needle placed in the source patient's artery or vein in a study of nurses in France [18]), a 2-tailed significance level of 5%, and a power level of 90%, the enrollment of 49 case patients and 196 control subjects was expected to permit detection of a minimal OR of 3 [19].

Data collection. For each case patient and control subject, demographic information and information concerning the characteristics of the exposure and of the source patient were collected with use of a standardized questionnaire translated into the language of each participating country. In each country, the questionnaires were filled in by a national investigator who had reviewed the incident reports that had been completed at the time of exposure. Because information for the source patient was not always available or known to the case patient or control patient at the time of exposure, it was obtained retrospectively by reviewing the medical records of the source patients.

Information about health care workers included age and sex. Information about exposure included the type of exposure (i.e., percutaneous injury or mucous membrane or skin contamination with infectious body fluid) and the body fluid to which the health care worker had been exposed (i.e., blood or other body fluids). For percutaneous injuries, information was collected about the device involved, the use of gloves, and the severity of the injury. Procedures involving a needle placed in the source patient's artery or vein (e.g., phlebotomy, insertion of an intravenous catheter, or collection of arterial blood gas) were distinguished from other procedures, such as injection into an intravenous catheter. The severity of injury was defined as superficial (surface scratch), moderate (penetration of the skin and bleeding), or deep (deep puncture or wound with bleeding). Information about the source patient included HCV RNA status (i.e., HCV RNA detection and HCV load), as well as hepatitis B virus and HIV status. Cut off values for HCV titer categories were determined using the distribution of HCV load in control subjects (HCV load 33rd and 66th percentiles).

Statistical analysis. MacNemar's χ^2 test and the Wilcoxon rank sum test for paired data were used to compare the unmatched general characteristics of case patients and control subjects. The crude disease "exposure" association was determined by estimating the OR and its 95% CI. This was done by univariate conditional logistic regression, to account for the matched design. OR significance was assessed by the Wald test [20].

When the *P* values for variables concerning demographic information, the type of exposure, and source patients were

<.25 in univariate analysis, they were submitted to a multivariate conditional logistic regression model [21]. Information concerning source patients' HCV RNA level was not introduced in this model because of the large proportion of missing data for this variable, which were seldom collected at the time of exposure. Backward stepwise regression procedures were used to identify the final multivariate model, and possible interactions were examined [21]. The goodness-of-fit of the model was assessed by using the logistic regression diagnostics procedure [22].

P values <.05 (2-tailed) were to be statistically considered significant. Statistical analyses were performed with SAS software, version 8.2 (SAS Institute).

RESULTS

The study population included 60 case patients (35 from France, 16 from Italy, 4 from Spain, 3 from the United Kingdom, and 2 from Switzerland) and 204 control subjects (110 from France, 64 from Italy, 12 from Spain, 9 from the United Kingdom, and 9 from Switzerland). The ratio of control subjects to case patients was less than 4:1, because in some centers, <4 control subjects were identified within 1 year of corresponding case's exposure. The distribution of case patients per year of exposure to HCV indicated an annual increase in the number reported between 1991 (when HCV antibody testing became available) and 1995, followed by a decrease during the period 1996–1997, and stability from 1998 through 2002 (figure 1).

In this study, all case patients were exposed to body fluids through percutaneous exposures (table 1). Of these exposures, 57 (95%) involved hollow-bore needles, and 3 (5%) involved solid needles or sharps. Fifty-nine case patients (98.3%) were exposed to blood, and 1 case patient was exposed to ascitic fluid. In contrast, 171 (83.8%) of 204 control subjects were exposed to body fluids through percutaneous exposure, and 32 (15.7%) were exposed through mucocutaneous exposures. One

hundred ninety control subjects (93.1%) were exposed to blood, and 12 were exposed to other body fluids.

Compared with the control subjects, the case patients were older (median age, 38 years vs. 35 years; *P* = .03), and more of them were male (30.0% vs. 18.6; *P* = .04). By univariate analysis, HCV infection was associated with injuries by hollow-bore needles (occurring in 95% of case patients, compared with 60.3% of control subjects; *P* < .0001), procedures involving needle placement in the source patient's vein or artery (occurring in 80.0% of case patients, compared with 38.2% of control subjects; *P* < .0001), and deep injuries (occurring in 56.6% of case patients, compared with 16.2% of control subjects; *P* < .0001) (table 1). There was no difference between case patients and control subjects regarding the use of gloves or the hepatitis B virus and HIV status of the source patient.

All 37 (100.0%) of the case patients for whom data on HCV RNA level were available were exposed to viremic source patients (i.e. source patients in whom HCV RNA was detected), compared with 42 (85%) of the 61 corresponding control subjects. Data on HCV load were available for 12 case patients and 27 control subjects. In unmatched univariate analysis, the risk of HCV transmission was found to be 11 times higher (95% CI, 1.1–114.1; *P* = .04) for health care workers who were exposed to source patients with an HCV load >6 log₁₀ copies/mL and 5.5 times higher (95% CI, 0.6–55.5; *P* = .15) for those exposed to source patients with a viral load of 4–6 log₁₀ copies/mL than it was for health care workers exposed to source patients with an HCV load <4 log₁₀ copies/mL (table 1).

In multivariate analysis, HCV transmission remained significantly associated with procedures involving hollow-bore needle placement in the source patient's vein or artery, the severity of injury, and the sex of the health care worker (table 2). Interaction terms were not included in this model, because they were not statistically significant on inclusion in the final model. The logistic regression diagnostics procedure showed

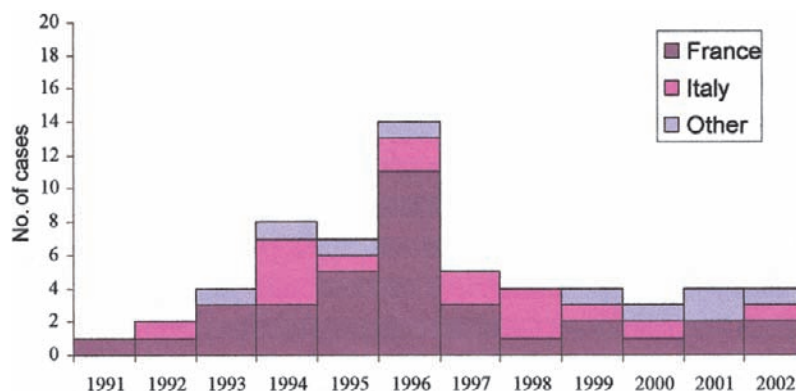


Figure 1. Distribution of cases of hepatitis C virus (HCV) transmission to health care workers by year of exposure to infectious blood or body fluids of HCV antibody-positive source patients and by country, 1991–2002.

Table 1. Analysis of risk factors for hepatitis C virus (HCV) seroconversion in health care workers who did (case patients) or did not (matched control subjects) experience HCV seroconversion after occupational exposure to HCV.

Variable	Case patients (n = 60)	Matched control subjects (n = 204)	Unadjusted matched OR (95% CI)	P
Type of exposure				
Percutaneous	60 (100)	171 (83.8)		
Body fluid contact with mucous membranes or skin	0 (0)	32 (15.7)		
Body fluid involved in exposure				
Blood	59 (98.3)	190 (93.1)	4.5 (0.5–43.5)	.20
Other body fluid	1 (1.7)	12 (5.9)	1.0	
Device involved in exposure ^a				
Suture needle	1 (1.7)	21 (10.3)	1.4 (0.1–25.3)	.80
Hollow-bore needle				
Not in vein or artery	9 (15.0)	45 (22.1)	5.1 (0.6–42.2)	.13
In vein or artery	48 (80.0)	78 (38.2)	20.3 (2.5–162.9)	.005
Other	2 (3.3)	27 (13.2)	1.0	
Severity of injury ^a				
Superficial	3 (5.0)	61 (29.9)	1.0	
Moderate	21 (35.0)	65 (31.7)	15.8 (2.1–122.5)	.008
Deep	34 (56.6)	34 (16.2)	57.6 (7.2–457.9)	.0001
Use of gloves				
Yes	32 (53.3)	111 (54.4)	1.0	
No	20 (33.3)	73 (35.8)	0.9 (0.5–1.9)	.843
Sex				
Female	41 (68.3)	156 (76.5)	1.0	
Male	18 (30.0)	38 (18.6)	2.2 (1.0–4.6)	.04
Age, median years (range)	38 (22–57)	35 (19–63)	1.0 (1.0–1.1)	.03
Source patient				
HIV status				
Negative	42 (70.0)	122 (59.8)	1.0	
Positive	12 (20.0)	41 (20.0)	0.9 (0.4–2.1)	.80
Hepatitis B virus status				
Negative	43 (71.6)	133 (65.2)	1.0	
Positive	6 (10.0)	14 (6.9)	2.1 (0.6–7.0)	.24
HCV load ^b				
≤4 log ₁₀ copies/mL	1 (1.7)	11 (5.4)	1.0	
>4 to 6 log ₁₀ copies/mL	5 (8.3)	10 (4.9)	5.5 (0.6–55.5)	.15
>6 log ₁₀ copies/mL	6 (10.0)	6 (2.9)	11.0 (1.1–114.1)	.04

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Data for case patients and control subjects may not total 60 and 204, respectively, because of missing data.

^a Analysis restricted to percutaneous exposures.

^b The matched design of the study was not considered in this analysis because of the large amount of missing data.

that the entire set of covariate patterns was correctly fitted by the final model.

DISCUSSION

In this study, conducted in 5 European countries from 1991 through 2002, occupational HCV transmission to health care workers was only found to occur after percutaneous exposure

to viremic blood or body fluids. In a multivariate conditional logistic regression model, in which the source patient's HCV load was not introduced, the risk of HCV transmission to a health care worker after percutaneous exposure increased for deep injuries and procedures involving hollow-bore needle placement in the source patient's vein or artery. Health care worker sex was also found to be independently associated with

Table 2. Multivariate conditional logistic regression analysis of risk factors for hepatitis C virus (HCV) transmission to health care workers after percutaneous exposure to HCV-infected body fluids.

Variable	Adjusted matched OR (95% CI)	P
Device involved in exposure		
Suture needle or other sharp object	1.0	
Hollow-bore needle		
Not in vein or artery	10.6 (0.9–128.4)	.063
In vein or artery	100.1 (7.3–1365.7)	.0005
Severity of injury		
Superficial	1.0	
Moderate	47.7 (2.3–974.1)	.01
Deep	155.2 (7.1–3417.2)	.001
Sex of health care worker		
Female	1.0	
Male	3.1 (1.0–10.0)	.056

HCV transmission, with an increased risk of transmission for men. In univariate analysis of data from a subset of case patients and control subjects, the risk of HCV transmission increased with the titer of HCV in the source patient, although we had to break the matched design of the study for this analysis because of the small numbers.

No data on factors that affect occupational HCV transmission to health care workers exist. To identify these factors, the present analysis assembled a database involving 60 case patients with documented occupational exposure to infectious body fluids from an HCV-positive source and evidence of HCV seroconversion in temporal association with the exposure. This represents a large data set in an area where data are scarce. We conducted an incident-matched case-control study and performed a multivariate conditional logistic regression analysis to identify independent risk factors for HCV transmission.

Our findings should nevertheless be interpreted with caution. Primarily, this study was a retrospective review of surveillance data obtained from different sources. Its retrospective design may have introduced bias in the estimation of the nature of exposures through either recall bias or misclassification. However, erroneous estimation of the nature of exposures related to recall bias is unlikely, because the data for most variables were collected through objective documentations derived from incident reports completed at the time of exposure. The only variables collected retrospectively were source patient's HCV RNA level and HBV and HIV status, which are objective variables that are less prone to recall bias. Misclassification bias may have affected some data, particularly subjective variables, such as the severity of injury. However, errors in determining these variables were probably not dependent on the case-control status of the health care workers, because the incident reports

were completed before those who drafted them knew whether the health care worker was a case patient or a control subject. Moreover, for both case patients and their matched control subjects, information about exposure was usually obtained by the same occupational health physician because of the matched design of the study; this physician probably tended to classify exposures in a self-consistent fashion. More importantly, the retrospective design of the study (and the fact that HCV RNA quantification for viremia was introduced on a widespread basis in Europe after 1995–1996 [23–25]) resulted in a high proportion of missing data when HCV RNA information concerning source patients was collected. Nevertheless, even with a small number of observations, we were able to show an association between HCV RNA titer and HCV transmission, but the matched design of the study was not applied to this analysis. In addition, because of the high proportion of missing values, we were not able to use the source patient HCV RNA status data in our final multivariate model. As a result, in this study, the effect of independent risk factors for HCV transmission was not adjusted to the HCV RNA status of the source patients.

In this study, occupational HCV transmission to health care workers was only found to occur after percutaneous exposures (not after mucocutaneous exposures). However, it is important to emphasize the fact that, although the largest proportion of HCV transmission to health care workers in our study occurred through percutaneous injuries, case reports have documented transmission of HCV as a result of splashes of blood from infected patients onto health care workers' mucous membranes [26–28]. Consequently, one should not reject mucocutaneous exposures as a potential source of HCV transmission. Moreover, the promotion of barrier protections, such as consistent use of appropriate eyewear (e.g., sealed protective goggles) that could prevent occupational infection from conjunctival exposure to bloodborne pathogens, should not be stopped in light of the results of our study.

The increased risk of occupational blood-borne pathogen transmission with deep injuries and after procedures involving hollow-bore needles has already been reported for HIV by Cardo et al. [29] in a case-control study involving health care workers who were occupationally exposed to HIV-infected blood. Our results for HCV transmission confirm that these factors probably represent indirect measures of inoculum volume. In injuries caused by hollow-bore needles, a larger volume of blood is transferred, and in procedures involving needle placement in the source patient's vein or artery, the needle contains undiluted blood.

The finding that HCV transmission only occurs after exposure to viremic patients is consistent with previous reports [30]. In a systematic review by Dore and colleagues of 29 studies (including studies of vertical transmission, transmission after transplantation, transfusion of blood components, and need-

lestick exposure), no case of HCV transmission was identified among subjects exposed to HCV RNA-negative sources [30]. Moreover, in our study, we found that the risk of transmission increased with the HCV RNA titer. This finding has already been reported for other transmission models, such as mother-to-infant transmission [31, 32], but has not been reported for occupational transmissions. However, this finding needs to be confirmed, first, because it was based on the small number of case patients and control subjects for whom the HCV RNA titer in the source patient was available, and second, because it was obtained by unmatched univariate analysis.

We observed an unexpected association between health care worker sex and HCV transmission. In several previous cohort studies, male sex was identified as an independent risk factor for HCV infection after adjustment, in particular, for transfusion history [33–35]. In addition, some studies found that male sex was associated with an increased risk of HCV infection during hemodialysis [36, 37], although this was not confirmed by others [38–40]. Nevertheless, we cannot rule out the possibility that the assessment of risk was affected by unidentified confounding variables or selection bias. Additional epidemiological and laboratory studies are therefore needed to confirm that the risk of HCV transmission is greater in men.

We did not find an association between the HIV status of the source patient and HCV transmission. Although anecdotal reports and surveillance studies of exposed health care workers—as well as the results of studies of vertical transmission—suggest that the frequency of HCV transmission increases when the source patient is coinfecting with HIV [41–46], other studies found conflicting results [6, 47, 48]. The interaction between these viruses is poorly understood. Additional studies are therefore needed to investigate the impact of HIV status on HCV transmission.

Differences between the systems for the surveillance of occupational infections within different countries (e.g., national vs. regional surveillance systems) resulted in differences between the number of case patients reported by the countries participating in the present study. Nevertheless, we observed an increase in the number of case patients with occupational HCV transmission reported annually from 1991 through 1995, followed by a decrease in 1996 and 1997 and a stable number since 1998. Although this result should be interpreted with caution because of the possible reporting bias, the overall increase observed from 1991 through 1995 was probably due to an improvement in occupational HCV infection surveillance systems. Regarding the overall decrease observed in 1996 and after, a similar decrease in the risk of percutaneous injury among health care workers, especially nurses, has been documented in France [18] (which country contributed about 60% of the case patients). This decrease was probably due to better compliance with universal, standard precautions and to the

introduction of needlestick-prevention devices on a wider scale, as demonstrated by several studies [49–51].

The results of the present study—and especially the identification of a higher risk of occupational transmission after percutaneous injuries with hollow-bore and blood-filled needles—highlight the need for widespread adoption of needlestick-prevention devices in health care settings (i.e., safety-engineered needle devices, such as intravenous catheters and blood-drawing devices), together with other preventive measures, such as education, to reduce the risk of occupational infection for health care workers. In addition, until new anti-HCV drugs (such as HCV serine protease inhibitors, which may eventually be used for postexposure prophylaxis) become available [52], the present results have important implications for the counseling and follow-up of health care workers after exposure. They suggest that, after occupational exposure to HCV, assessment of the risk of transmission should take into account the severity of the injury, the device involved, and the HCV RNA status of the source patient. Following this assessment, health care workers at low risk for transmission should be fully informed of this fact, because such information would, no doubt, substantially reduce the anxiety caused by their injury. Follow-up schedules based on the results of anti-HCV antibody testing could then be proposed to health care workers who are at low risk. For health care workers experiencing high-risk exposures, follow-up schedules based on alanine transaminase monitoring, as currently recommended by European guidelines [17, 53], or HCV RNA testing may be proposed; if acute HCV infection is detected, adequate treatments may be initiated, although the ideal timing and regimen of antiviral therapy remain to be defined. However, these follow-up strategies and the frequency of postexposure testing need to be further investigated through well-designed cost-effectiveness studies.

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